

Article

Synthesis of Benzyl 4-Hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoate - The Aromatic Unit of Calicheamicin γ_1^I

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Ácido orselínico é benzilado e 4-benziloxi-2-hidroxi-6-metilbenzoato de benzila (**7**) é então convertido no composto desejado (**2**), o qual é o constituinte aromático de calicheamicin γ_1^I .

Orsellinic acid (**6**) was benzylated, and the benzyl 4-benzyloxy-2-hydroxy-6-methylbenzoate (**7**) was then elaborated into the title compound (**2**), which is the aromatic constituent of calicheamicin γ_1^I .

Keywords: *calicheamicin γ_1^I , antitumour, orsellinic acid*

Introduction

Calicheamicin γ_1^I is a highly sophisticated molecule that displays high antitumour and antibiotic potency and an unusual mode of action¹.

Nicolaou *et al.*² used compound (**1**) as an intermediate in the synthesis of calicheamicin γ_1^I . Nevertheless after coupling the monossacaride to the free hydroxyl of (**1**), they needed three steps to convert the methyl ester into the corresponding carboxylic acid.

In this work we describe the synthesis of benzyl 4-hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoate (**2**) from the readily available 3,5-dimethoxytoluene (**3**).

The benzyl ester (**2**) should be a better intermediate for the synthesis of calicheamicin γ_1^I than the methyl ester (**1**), as the benzyl group can be easily removed by hydrogenation without deprotecting the carbohydrate bound to the free oxygen.

Experimental

Reagents and solvents were purified when necessary according to the usual procedures described in the literature³. Flash column chromatography was performed using Crosfield Sorbil C60 (32-63 μm). Rf's were determined by Analytical Thin Layer Chromatography on a 0.25 mm film of silica gel containing fluorescent indicator UV₂₅₄ sup-

ported on a plastic sheet (CamLab plc.). The melting points were determined on an Electrothermal digital apparatus without correction. Infrared Spectra were recorded on a Perkin Elmer 881 grating spectrometer, scanning from 625 to 4000 cm^{-1} . The samples were run as nujol mull. Mass Spectra were recorded on a MICROMASS 7070F. ¹H and ¹³C-NMR spectra were recorded on a JEOL JNM-EX400 (400 and 100.53 MHz) and on a Bruker WH250 (250 and 62.89 MHz). They were recorded in CDCl₃ and tetramethylsilane was used as the internal standard.

*Benzyl 4-benzyloxy-2-hydroxy-6-methylbenzoate (**7**) and Benzyl 2,4-dibenzyloxy-6-methylbenzoate (**8**)*

To a mixture of orsellinic acid (**6**) (5.0 g, 29.7 mmol) and anhydrous potassium carbonate (15.0 g, 108.5 mmol) in dry acetone (150 mL) was added benzyl bromide (14.0 g, 81.9 mmol). The mixture was stirred under reflux in an atmosphere of argon for 7 h. The heating was removed and the mixture was poured into 2 M hydrochloric acid (500 mL). The mixture was extracted with petrol-diethyl ether 4:6 (4 x 200 mL) and the combined organic layers dried (MgSO₄), filtered and evaporated to dryness. The white crystalline residue was mixed with silica gel and purified by column chromatography eluting with petrol-diethyl ether 8:2. The dibenzyl compound was obtained as white

crystalline needles (4.3 g, MW 348.398, 42%) and the tribenzyl as white crystalline plates (7.6 g, 58%).

Compound 7

R_f 0.49 (petrol-diethyl ether 8:2); **m.p.** 78 °C; δ_{H} (250 MHz; CDCl₃; J/Hz) 2.49 (s, 3 H, ArCH₃), 5.05 (s, 2 H, CH₂, Bn), 5.38 (s, 2 H, CH₂, Bn), 6.30-6.45 (m, 2 H, ArH), 7.30-7.50 (m, 10 H, 2 x Bn); δ_{C} (62.9 MHz; CDCl₃) 24.6 (ArCH₃), 67.0 (CH₂), 69.9 (CH₂), 99.8, 111.8 (C-3, -5), 127.4, 128.1, 128.4, 128.6 (Bn), 135.4 (C-1, Bn), 136.2 (C-1, Bn), 143.2 (C-6), 163.1, 165.6 (C-2, -4), 171.4 (C=O); (**found**: 348.1353. C₂₂H₂₀O₄ **requires**, 348.1362).

Compound 8

R_f 0.31 (petrol-diethyl ether 8:2); **m.p.** 93 °C; δ_{H} (250 MHz; CDCl₃; J/Hz) 2.25 (s, 3 H, ArCH₃), 5.00 (s, 2 H, CH₂, Bn), 5.02 (s, 2 H, CH₂, Bn), 5.30 (s, 2 H, CH₂, Bn), 6.35-6.45 (m, 2 H, ArH), 7.25-7.45 (m, 15 H, 3 x Bn); δ_{C} (62.9 MHz; CDCl₃) 19.9 (ArCH₃), 66.7 (CH₂), 70.0 (CH₂), 70.4 (CH₂), 98.4, 108.2 (C-3, -5), 117.1, 127.0, 127.3, 127.7, 128.0, 128.3, 128.4, 128.5 (Bn), 135.9, 136.5, 136.6 (3 x CH₂, Bn), 138.4 (C-6), 157.3, 160.4 (C-2, -4), 167.9 (C=O).

Benzyl 4-benzyloxy-2-hydroxy-3-formyl-6-methylbenzoate (9)

A 1.0 M dichloromethane solution of titanium (IV) chloride (75 mL, 75 mmoles) was added dropwise to a vigorously stirred cooled (-10 °C) solution of the dibenzyl (7) (10.37 g, 29.8 mmoles) and dichloromethyl methyl ether[#] (7.5 g, 65.2 mmoles) in dry dichloromethane (150 mL) under argon atmosphere. Stirring was continued for a further 3 h at 0 °C, and then poured into ice-cold hydrochloric acid (500 mL). The resulting suspension was transferred to a separating funnel and the layers separated. The aqueous layer was extracted with diethyl ether-petrol 6:4 (3 x 350 mL). The dichloromethane was evaporated under vacuum and the residue was combined with the ether-petrol layers. The organic mixture was washed with water (2 x 100 mL), filtered through a pad of silica gel, and the silica washed with diethyl ether (500 mL). The solvent was removed on the rotary evaporator and the residue dried under high vacuum to give a red solid which was used without any further purification (10.0 g, 89%).

R_f 0.27 (petrol-diethyl ether 6:4); ν (nujol mull)/cm⁻¹ 1727 (C=O, ester) and 1637 (C=O, aldehyde); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.32 (s, 3 H, ArCH₃), 5.15 (s, 2 H, CH₂, Bn), 5.38 (s, 2 H, CH₂, Bn), 6.30 (s, 1 H, ArH), 7.30-7.50 (m, 10 H, Bn), 10.30 (s, 1 H, CHO).

Benzyl 4-benzyloxy-2,3-dihydroxy-6-methylbenzoate (10)

A solution of the aldehyde (9) (9.5 g, 25.2 mmoles) in a mixture of dioxane (150 mL) and 40% sodium hydroxide

(7 mL) was stirred and cooled in an ice bath under argon atmosphere. Hydrogen peroxide (30%, 60 mL) in dioxane (120 mL) was added dropwise using a pressure equalizer dropping funnel. The cooling bath was removed and after stirring for a further 1 h the solution was poured into ice-cold 2 M hydrochloric acid (250 mL) and extracted with diethyl ether (3 x 200 mL). The combined ether layers were washed with water (2 x 100 mL) and brine (2 x 100 mL) and dried (MgSO₄). The solvent was removed and the oily residue filtered through a pad of silica gel to give a yellow oil (8.8 g, 96%).

R_f 0.27 (petrol-diethyl ether 6:4); ν (nujol mull)/cm⁻¹ 3469 (OH), 1653 (C=O); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.45 (s, 3 H, ArCH₃), 5.18 (s, 2 H, CH₂, Bn), 5.40 (s, 2 H, CH₂), 5.45 (s, 1 H, OH), 6.35 (s, 1 H, ArH), 7.30-7.50 (m, 10 H, 2 x Bn).

Benzyl 4-benzyloxy-2,3-dimethoxy-6-methylbenzoate (11)

A mixture of potassium carbonate (14.0 g, 102.8 mmoles), the catechol (10) (8.6 g, 23.6 mmoles) and dimethyl sulphate (10.0 g, 79.3 mmoles) in dry acetone (250 mL) was refluxed for 5 h under argon atmosphere. The heating was removed and after 10 min it was filtered under vacuum using a sinter funnel and the solid was washed with acetone. The filtrate was evaporated to dryness in the rotary evaporator and the residue was dissolved in diethyl ether-petrol 2:8. The solution was loaded onto a column with silica gel and eluted with the same solvent mixture to give the title compound as a crystalline solid (7.7 g, 83%).

R_f 0.51 (petrol-diethyl ether 6:4); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.20 (s, 3 H, ArCH₃), 3.84, 3.86 (2s, 2 x 3 H, 2 x OCH₃), 5.10 (s, 2 H, CH₂, Bn), 5.35 (s, 2 H, CH₂, Bn), 6.50 (s, 1 H, ArH), 7.30-7.50 (m, 10 H, 2 x Bn); (**found**: 392.1602. C₂₄H₂₄O₅ **requires**, 392.1624).

4-Hydroxy-2,3-dimethoxy-6-methylbenzoic acid (12)

A mixture of the dibenzyl (11) (4.5 g, 11.5 mmoles) and 5% palladium on carbon (0.7) in ethyl acetate (100 mL) under an atmosphere of hydrogen was stirred overnight. The mixture was filtered and the palladium washed with ethyl acetate. The combined organic washings were evaporated under vacuum to give a yellow oil (2.33 g, 96%).

R_f 0.10 (petrol-diethyl ether 6:4); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.25 (s, 3 H, ArCH₃), 3.80, 3.88 (2s, 2 x 3 H, 2 x OCH₃), 6.54 (s, 1 H, OH), 8.28 (broad s, 1 H, OH).

[#] Dichloromethyl methyl ether is highly toxic lachrymator

Benzyl 4-hydroxy-2,3-dimethoxy-6-methylbenzoate (13)

A mixture of the acid-phenol (**12**) (0.48 g, 2.26 mmoles), anhydrous potassium carbonate (0.40 g, 2.89 mmoles) and benzyl bromide (0.40 g, 2.34 mmoles) in dry acetone (20 mL) was stirred overnight at room temperature under argon atmosphere. The mixture was poured into ice cold 2 M hydrochloric acid (40 mL) and was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL) and dried (MgSO₄). The ether was removed under vacuum and the residue purified by column chromatography eluting with petrol-diethyl ether 7:3 to give the benzyl ester as an oil (0.15 g, 22%).

R_f 0.30 (petrol-diethyl ether 6:4); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.20 (s, 3 H, ArCH₃), 3.79, 3.87 (2s, 2 x 3 H, 2 x OCH₃), 5.35 (s, 2H, CH₂, Bn), 5.92 (s, 1 H, OH), 6.54 (s, 1H, ArH), 7.33-7.46 (m, 5 H, ArH, Bn). δ_{C} (100 MHz; CDCl₃) 19.4 (ArCH₃), 60.8, 61.2 (2 x OCH₃), 67.0 (CO₂CH₂), 112.4 (C-5), 120.5 (C-1), 128.3, 128.5, 128.6 (Bn, o, m, p), 132.5 (C-6), 135.8 (C-3), 137.5, 150.5 (C-2, -4), 167.5 (C=O); (**found**: 302.1167. C₁₇H₁₈O₅ **requires**, 302.1154).

Methyl 4-hydroxy-2,3-dimethoxy-6-methylbenzoate (16)

A mixture of the acid-phenol (2.0 g, 9.42 mmoles), anhydrous potassium carbonate (1.5 g, 10.85 mmoles) and dimethyl sulphate (1.2 g, 9.51 mmoles) in dry acetone (50 mL) was stirred overnight at room temperature under argon atmosphere. The mixture was poured into ice cold 2 M hydrochloric acid (80 mL) and was extracted with diethyl ether (3 x 80 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL) and dried (MgSO₄). The organic mixture was filtered through a pad of silica and the silica was rinsed with a further 100 mL of diethyl ether-petrol 1:1. The solvent was removed under vacuum to give (**16**) as a solid (1.8 g, 84%).

R_f 0.48 (petrol-diethyl ether 6:4); **m.p.** 77 °C; ν (nujol mull)/cm⁻¹ 3399 (OH), 1710 (C=O); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.23 (s, 3 H, ArCH₃), 3.87 (2s, 6 H, 2 x OCH₃), 3.89 (s, 3 H, OCH₃) 6.12 (s, 1 H, OH), 6.55 (s, 1 H, ArH).

Methyl**4-hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoate (1)**

1.0 M solution of iodine chloride in dry dichloromethane (15.0 mL) was added dropwise to a stirred solution of the methyl benzoate (**16**) (2.55 g, 11.3 mmoles) in dry dichloromethane (50 mL). The mixture was stirred for 5 h, diluted with dichloromethane (100 mL) and washed with aqueous Na₂S₂O₃ (2 x 30 mL), and water (1 x 30 mL). The organic layer was dried (MgSO₄) and the solvent evaporated. The residue was dissolved in petrol-ethyl acetate 1:2 (100 mL), filtered over a short column of silica gel and washed with petrol-ethyl acetate 1:2 (100 mL). The

solvent was evaporated and the residue recrystallized from toluene-petrol to afford (**1**) as a white crystalline solid (2.56 g, 64%). The solvent of the filtrate was removed and the residue purified by column chromatography to give a further (0.80 g, 20%) of the iodo methyl ester.

R_f 0.28 (petrol-diethyl ether 6:4); **m.p.** 137-138 °C; δ_{H} (250 MHz; CDCl₃; J/Hz) 2.36 (s, 3 H, ArCH₃), 3.88, 3.91, 3.91 (3s, 3 x 3 H, 2 x OCH₃, COOCH₃), 6.38 (s, 1 H, OH); δ_{C} (62.9 MHz; CDCl₃) 25.2 (ArCH₃), 52.4 (CO₂Me), 61.0, 61.4 (2 x OCH₃), 84.0 (C-5), 121.8 (C-1), 134.1, 136.6 (C-3, -6), 149.6, 150.5 (C-2, -4), 167.7 (C=O); (**found**: C, 37.66; H, 3.73; I, 36.88. C₁₁H₁₃O₅I **requires**, C, 37.52; H, 3.72; I, 36.04).

4-Hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoic acid (17)

A solution of the iodo methyl ester (**1**) (0.4 g, 1.136 mmoles) in 2.5 M aqueous sodium hydroxide (20 mL) was refluxed for 3 h. The reaction mixture was poured into ice-cold 2 M hydrochloric acid (50 mL) and then extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and dried (MgSO₄). The solvent was evaporated under vacuum and the residue was left under high vacuum for 6 h to give the free acid as a white crystalline solid (0.35 g, 91%).

R_f 0.10 (petrol-diethyl ether 6:4); **m.p.** 63 °C; δ_{H} (250 MHz; CD₃CN; J/Hz) 2.55 (s, 3 H, ArCH₃), 3.95, 3.96 (2s, 2 x 3 H, 2 x OCH₃), 6.5 (broad s, 1 H, OH).

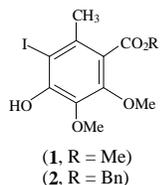
Benzyl**5-iodo-4-hydroxy-2,3-dimethoxy-6-methylbenzoate (2)**

Benzyl bromide (0.2 g, 1.17 mmoles) was added by pipette to a stirred mixture of the iodo-carboxylic acid (**17**) (0.34 g, 1.01 mmoles) and anhydrous potassium carbonate (0.2 g, 1.45 mmoles) in dry acetone (20 mL) under argon atmosphere. The mixture was stirred overnight and was poured into ice-cold 2 M hydrochloric acid (50 mL). The mixture was extracted with diethyl ether (4 x 50 mL), dried (MgSO₄), evaporated to dryness under vacuum and the residue purified by column chromatography eluting with petrol-diethyl ether 7:3 to give the iodo benzyl ester as an oil (0.3 g, 70%).

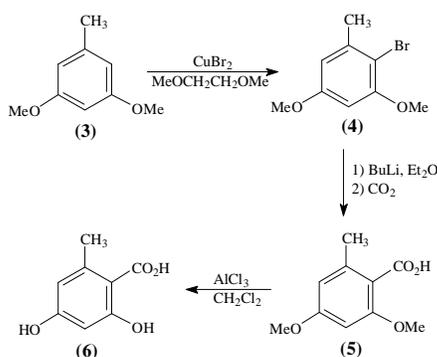
R_f 0.36 (petrol-diethyl ether 6:4); δ_{H} (250 MHz; CDCl₃; J/Hz) 2.32 (s, 3 H, ArCH₃), 3.78, 3.88 (2s, 2 x 3 H, 2 x OCH₃), 5.36 (s, 2 H, CH₂, Bn), 6.43 (s, 1 H, OH), 7.34-7.45 (m, 5 H, ArH, Bn); δ_{C} (62.9 MHz; CDCl₃) 25.1 (ArCH₃), 61.0, 61.2 (2 x OCH₃), 67.2 (CO₂CH₂), 84.0 (C-5), 121.7 (C-1), 128.2, 128.4, 128.5 (Bn, o, m, p), 134.1, 135.4 (C-2, -6), 136.5 (C-1, Bn), 149.6, 150.4 (C-2, -4), (C=O); (**found**: 428.0109. C₁₇H₁₇O₅I **requires**, 428.0121).

Results and Discussion

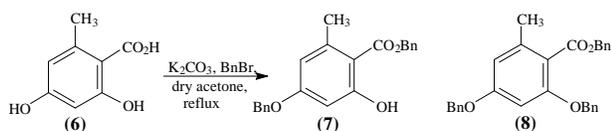
The benzyl group is easily removed by hydrogenation in the presence of palladium on carbon. We envisaged the synthesis of benzyl 4-hydroxy-5-iodo-2,3-dimethoxy-6-methylbenzoate (**2**) as a potential intermediate for the synthesis of calicheamicin γ_1 ¹.



Orsellinic acid (**6**) was prepared in three steps in high yield from the readily available 3,5-dimethoxytoluene (**3**) following the literature procedure⁴.



Benzylation of orsellinic acid with benzyl bromide in the presence of anhydrous potassium carbonate in dry acetone under reflux gave the di (**7**) and tribenzylated (**8**) adducts in 42% and 58% yield respectively.

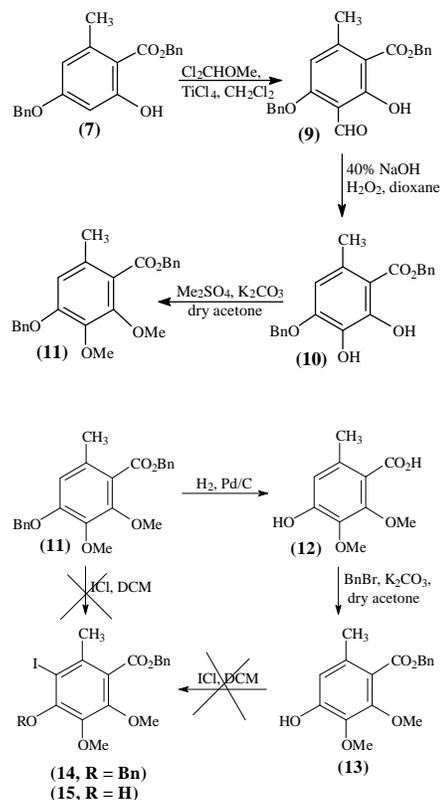


The tribenzylated compound (**8**) can be converted quantitatively back into starting material (**6**) by hydrogenation in the presence of palladium on carbon.

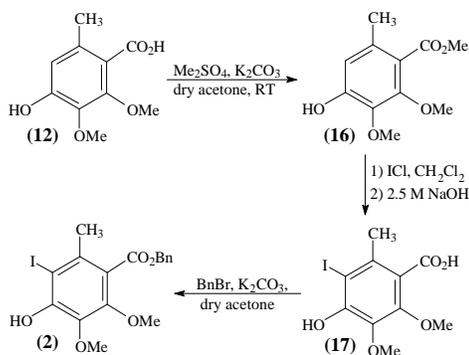
Benzyl 4-benzyloxy-2-hydroxy-6-methylbenzoate (**7**) was selectively formylated with dichloromethyl methyl ether and titanium tetrachloride in the ortho position in 89% yield⁵. The aldehyde (**9**) was oxidised to the corresponding catechol (**10**) with hydrogen peroxide (96% yield)^{6,7}. Methylation of (**10**) with dimethyl sulphate gave the dimethoxy compound (**11**) in 83% yield.

The two benzyl groups were removed by catalytic hydrogenation in quantitative yield. Compound (**12**) was then monobenzylated with benzyl bromide at room temperature in the presence of the free phenol. Nevertheless

attempts to iodinate the benzyl esters (compounds **11** and **13**) with iodine chloride to produce compounds (**14** and **15**) failed.



Methylation with dimethyl sulphate in dry acetone in the presence of anhydrous potassium carbonate of (**12**) gave the methyl ester (**16**). The literature procedure was followed to iodinate and hydrolyse the methyl ester (**16**) to produce (**17**)⁸. Finally, compound (**17**) was benzylated with benzyl bromide in dry acetone in the presence of potassium carbonate in 70% yield to give the title compound (**2**).



Acknowledgements

E.S. de Alvarenga thanks the Yamanouchi Research Institute for a Research Fellowship.

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Received: April 30, 1998